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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,994	07/24/2006	Stephen J. Beebe	113019172US4	7183

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EXAMINER
SHEN, WU CHENG WINSTON

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,994	BEEBE ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-132* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-132 are pending in the instant application.

This application 10/564,994 is a 371 of PCT/US04/23078 filed on 07/19/2004 which claims benefit of 60/487,932 filed on 07/18/2003, and claims benefit of 60/499,921 filed on 09/04/2003, and claims benefit of 60/526,585 filed on 12/04/2003.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1, 2, 6-17, 23-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry of the agent into the nucleus, wherein the agent is a nucleic acid.

II. Claims 1, 2, 17, 19, 23-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry

of the agent into the nucleus, wherein the agent is a protein, a peptide, or a polypeptide, wherein the agent is *an antigen*.

III. Claims 1, 2, 18, 23-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry of the agent into the nucleus, wherein the agent is a protein, a peptide, or a polypeptide, wherein the agent is *not an antigen*.

IV. Claims 1, 2, 20, 23-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry of the agent into the nucleus, wherein the agent is a protein, a peptide, or a polypeptide, wherein the agent is an *antibody*.

V. Claims 1-3, and 23-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry of the agent into the nucleus, wherein the agent is a drug, wherein the drug is *an antibiotic*.

VI. Claims 1, 2, 4, 5, and 23-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry of the agent into the nucleus, wherein the agent is a drug, wherein the drug is *a chemotherapeutic agent*.

VII. Claims 1, 2, 21-33, drawn to a method for introducing an agent into a cell comprising providing a preparation comprising the cell and agent, and applying the nanosecond pulse electric fields to said preparation, which facilitates the entry of the agent into the nucleus, wherein the agent is *a cytotoxic agent*.

VIII. Claims 34-41, drawn to a method of enhancing gene expression in a cell comprising providing a preparation comprising the cell and the nucleotide sequence to be delivered into the cell, and applying nanosecond pulse electric fields to said preparation, wherein said application facilitates the entry of the agent into the nucleus.

IX. Claims 42-55, drawn to a method of enhancing gene expression in a cell comprising transfecting said cell with the desired gene and applying nanosecond pulse electric fields to said cell.

X. Claims 56-66, drawn to a method of enhancing gene expression in a cell comprising applying one or more long pulses to said cell and applying one or more nanosecond pulse electric field pulses to said cell.

XI. Claims 67-77, 81-84, 89-93, drawn to a pulse generator for generating electrical pulses comprising: a first circuit for generating a first pulse having a long duration and low voltage amplitude; a second circuit for generating a second pulse having a short duration and high voltage amplitude; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse.

XII. Claims 78-80, drawn to a pulse generator for generating electrical pulses comprising: a first circuit for generating a first pulse having a long duration and low voltage amplitude; a second circuit for generating a second pulse having a short duration and high voltage amplitude; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse, wherein the pulse generator further comprising a delivery apparatus for delivering said first pulse and said second pulse to a load.

XIII. Claims 85-88, drawn to a pulse generator for generating electrical pulses comprising: a first circuit for generating a first pulse having a long duration and low voltage amplitude; a second circuit for generating a second pulse having a short duration and high voltage amplitude; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse, wherein the pulse generator further comprising a first switch coupled to and controlled by said control circuit, said first switch being operable to couple and decouple the first circuit from a load.

XIV. Claims 94-106, drawn to a pulse generator for generating electrical pulses comprising: first generator means for generating a first pulse having a long duration and low voltage amplitude; second generator means for generating a second pulse having a short duration and high voltage amplitude; and control means for controlling timing of the pulses generated by said first generator means and said second generator means.

XV. Claims 107-114, drawn to a method of enhancing gene expression using a pulse generator, the method comprising the sequential, the non-sequential, and the sequence independent steps of: triggering a first pulse having a long duration and low voltage amplitude from a first circuit of the pulse generator; delivering the first pulse to at least one cell to cause electroporation at the plasma membrane of the at least one cell; triggering a second pulse having a long duration and low voltage amplitude from a second circuit of the pulse generator; and delivering the second pulse to the at least one cell to cause electroporation at the nuclear membrane of the at least one cell.

XVI. Claim 115, drawn to a method of enhancing gene expression in a cell using a multi-pulse generator, the method comprising the sequential, the non-sequential, and the sequence independent steps of: charging a capacitor; triggering a high voltage, high current transistor to initiate discharge of the charge accumulated in the capacitor into at least one cell to cause electroporation at the plasma membrane of the at least one cell; triggering the high voltage, high current transistor to stop the discharge of the capacitor after a predetermined long duration; actuating a switch to decouple the capacitor from the at least one cell; charging a transmission line; triggering a high voltage switch to initiate discharge of the charge accumulated in the transmission line into the at lest one cell to cause electroporation at the nuclear membrane of the at least one cell; and triggering the high voltage switch to stop discharge of the transmission line after a predetermined short duration.

XVII. Claim 116, drawn to a multi-pulse generator for causing electroporation at both a cellular plasma membrane and a nuclear membrane, said multi-pulse generator comprising: means for triggering a first pulse having a long duration and low voltage amplitude; means for delivering said first pulse to at least one cell, said first pulse causing electroporation at the plasma membrane of the at least one cell; means for triggering a second pulse having a short duration and high voltage amplitude; and means for delivering the second pulse to the at least one cell, said second pulse causing electroporation at the nuclear membrane of the at least one cell.

XVIII. Claim 117, drawn to a multi-pulse generator for enhancing gene expression in a cell, said multi-pulse generator comprising: means for accumulating a charge; means for selectively discharging the accumulated charge into at least one cell to cause electroporation at the plasma membrane of the at least one cell, and terminating discharge of the accumulated charge; means for charging a transmission line; and means for selectively discharging said transmission line into the at least one cell to cause electroporation at the nuclear membrane of the at least one cell, and terminating discharge of the transmission line.

XIX. Claim 118, drawn to a dual-pulse generator for enhancing gene expression in a cell, said dual-pulse generator comprising: a first pulse generator for generating a first pulse having a long duration and low voltage amplitude, said first pulse causing electroporation of the cellular plasma membrane of the cell; a second pulse generator for generating a second pulse having a short duration and high

voltage amplitude, said second pulse causing electroporation of the nuclear membrane of the cell; and a control circuit for controlling timing of pulses generated by said first pulse generator and said second pulse generator.

XX. Claim 119, drawn to a dual-pulse generator for enhancing gene expression in a cell, the dual-pulse generator comprising: first generator means for generating a first pulse having a long duration and low voltage amplitude, said first pulse causing electroporation of the cellular plasma membrane of the cell; second generator means for generating a second pulse having a short duration and high voltage amplitude, said second pulse causing electroporation of a nuclear membrane of the cell; and control means for controlling timing of the pulses generated by said first generator means and said second generator means.

XXI. Claim 120, drawn to a dual-pulse generator for enhancing gene expression in a cell, the dual-pulse generator comprising: a first high voltage power supply; a first charging resistor coupled to said first high voltage power supply; a capacitor coupled at a first end to said first charging resistor and coupled at a second end to a load; a transistor coupled to the second end of the first charging resistor and the first end of the capacitor, said transistor controlling electrical discharge of the capacitor to said load; a second high voltage power supply; a second charging resistor coupled to said second high voltage power supply; a transmission line coupled at a first end to said second charging resistor and coupled at a second end to the load; a control circuit for controlling electrical discharge of said capacitor and said transmission line; a first switch for selectively coupling and decoupling

said capacitor from the load; a first trigger unit coupled to said control circuit and said first switch, said first trigger unit actuating said first switch responsive to one or more commands received from said control circuit; a second switch for selectively discharging said transmission line; a second trigger unit coupled to said control circuit and said second switch, said second trigger unit actuating said first switch responsive to one or more commands received from said control circuit; and a delivery apparatus for delivering the electrical discharges from said capacitor and said transmission line to the load.

XXII. Claim 121, drawn to a method of enhancing gene expression using a dual-pulse generator, the method comprising the sequential, the non-sequential, and the sequence independent steps of: triggering a first pulse type from the dual-pulse generator, the first pulse type having a long duration and low voltage amplitude; delivering the first pulse type to at least one cell to cause causes electroporation at the plasma membrane of the at least one cell; waiting a predetermined time interval; triggering a second pulse type from the dual-pulse generator, the second pulse type having a short duration and high voltage amplitude; and delivering the second pulse type to the at least one cell to cause electroporation at the nuclear membrane of the at least one cell.

XXIII. Claims 122-127, drawn to a method of applying a nanosecond pulse electric field to a patient in need thereof.

XXIV. Claims 128-132, drawn to a method of enhancing gene expression in a cell comprising applying a nanosecond pulse electric field to said cell.

3. The inventions listed as Groups I-XXIV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Applicant's claims encompass multiple inventions, multiple products (various pulse generators with distinct components) and multiple methods (methods for introducing various patentably distinct agents --- a nucleic acid, a protein, an antibody, a chemotherapeutic agent, a cytotoxic agent etc, methods for enhancing gene expression with different recited steps, methods of applying a nanosecond pulse electric field to a patient), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. Furthermore, there is no common technical feature shared by Groups I-XXIV.

4. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

(i) The species are as follows: bleomycin, daunomycin, 5-FU, cytosine arabinoside, colchicine, cytochalasin B, daunorubicin, neocarcinostatin, suramin, doxorubicin, carboplatin, taxol, mitomycin C, vincristine, vinblastine, methotrexate, and cisplatin, and a specific combination thereof (claim 5). The following claim(s) are generic: claim **4**.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special

technical features for the following reasons: they are distinct chemotherapeutic agents with different structures and functions that underlie their therapeutic effects.

(ii) The species are as follows: ricin, abrin, diphtheria toxin, and saporin (claim 22). The following claim(s) are generic: claim **21**.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: they are distinct cytotoxic agents with different structures and functions that underlie their cytotoxic effects.

(iii) The species are as follows: eukaryotic cells, prokaryotic cells, fat cells, bone cells, vascular cells, muscle cells, cartilage cells, bacterial cells, and a specific combination thereof (claim 23). The following claim(s) are generic: claim **1**.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: they are distinct cells with distinct subcellular structures/organizations (presence or absence of nuclear membrane, cell wall etc) and different feasibility for entrance of various agents.

(iv) The species are as follows: adenocarcinoma, squamous carcinoma, carcinoma of the organs, sarcoma, chondrosarcoma, melanosarcoma, leukemia, lymphoma, acute lymphomatic leukemia, acute myelogenous leukemia, non-Hodgkin's lymphoma, Burkitt's lymphoma, B-cell lymphoma, and T-cell lymphoma (claim 25). The following claim(s) are generic: claim **24**.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special

technical features for the following reasons: they are distinct cancer cells with distinct pathological characteristic, underlying causes, and potential treatments.

(v) The species are as follows: adenovirus vector, a herpes virus vector, a vaccinia vector, and a retroviral vector (claim 53). The following claim(s) are generic: claim **52**.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: they are distinct viral vectors with distinct genomic structures (DNA or RNA genome etc) and different cloning capacity, and tropism for targeting cells.

Applicant is required, in reply to this action, to elect a single species, for each of **(i)** to **(v)** listed above), to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

5. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction were not required because the

inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103 (a) of the other invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-

3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632